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TITLE PAGE

Title

Tobacco smoking cessation and improved gastroesophageal reflux. A prospective population-based cohort study: the HUNT study

Running head

Tobacco smoking and gastroesophageal reflux

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ABSTRACT

Objective Tobacco smoking increases the risk of gastroesophageal reflux symptoms (GERS), but whether tobacco smoking cessation improves GERS is unclear. The aim of this study was to clarify if tobacco smoking cessation improves GERS.

Design The study was based on the Nord-Trøndelag health study (the HUNT study), a prospective population-based cohort study conducted from 1995-1997 to 2006-2009 in Nord-Trøndelag County, Norway. All residents of the county from 20 years of age were invited. The study included 29,610 individuals (61% response rate) who reported whether they had heartburn or acid regurgitation. The association between tobacco smoking cessation and improvement in GERS was assessed by logistic regression, providing odds ratios (ORs) with 95% confidence intervals (CIs). The analyses were stratified by antireflux medication, and the results were adjusted for sex, age, body mass index (BMI), alcohol consumption, education, and physical exercise. Subgroup analyses were also stratified by BMI.

Results Among individuals using antireflux medication at least weekly, cessation of daily tobacco smoking was associated with improvement in GERS from severe to no or minor complaints (adjusted OR 1.78, 95% CI 1.07 to 2.97), compared with persistent daily smoking. This association was present among individuals within the normal range of BMI (OR 5.67, 95% CI 1.36 to 23.64), but not among overweight individuals. There was no association between tobacco smoking cessation and GERS status among individuals with minor GERS or individuals using antireflux medication less than weekly.

Conclusion Tobacco smoking cessation was associated with improvement in severe GERS only in individuals of normal BMI using antireflux medication at least weekly, but not in other individual with GERS.

STUDY HIGHLIGHTS

1) What is current knowledge

- Gastroesophageal reflux symptoms (GERS) are prevalent in Western populations and associated with reduced health related quality of life and increased risk of esophageal adenocarcinoma.
- Tobacco smoking is associated with an increased the risk of GERS.
- The effect of tobacco smoking cessation on GERS is not clear.

2) What is new here

- This study did not find any association between tobacco smoking cessation and improvement in GERS in individuals not using regular antireflux medication.
- Tobacco smoking cessation was associated with an improvement in severe GERS in individuals of normal weight using regular antireflux medication.
- Tobacco smoking cessation was associated with an increased chance of treatment success with regular use of antireflux medication in severe GERS.
- This study suggests that tobacco smoking cessation might be beneficial in normal weight patients suffering from gastroesophageal reflux.

MANUSCRIPT TEXT

INTRODUCTION

Tobacco smoking is associated with an increased risk of gastroesophageal reflux symptoms (GERS) according to several population-based studies from Western countries.(1-9) The odds ratios (ORs) of GERS among smokers compared to non-smokers have been in the range of 1.3 to 2.5. Tobacco smoking increases the risk of GERS by reducing the lower esophageal sphincter pressure, facilitating gastric acid to reach the esophagus,(10-12) and reducing the salivary bicarbonate secretion, which neutralizes the acidity of the gastric contents.(13, 14) In addition, both GERS and tobacco smoking are independently associated with an increased risk of adenocarcinoma of the esophagus and esophagogastric junction.(15-19) Two recent reviews on the effect of lifestyle changes on gastroesophageal reflux disease (GERD) concluded that the evidence to date does not support an improvement in GERD after cessation of tobacco use.(20, 21) However, in the available studies, only the very short-term effect of smoking cessation on GERD outcomes was evaluated.(22-24) Our hypothesis is that tobacco smoking cessation improves GERS. The aim of this study was to clarify if there is an association between tobacco smoking cessation and improvement in GERS in a large and population-based study with long follow-up.

METHODS

Study design, setting and participants

The study was based on a large population-based health study, the Nord-Trøndelag health study (the HUNT study), which we have used previously for epidemiological studies of GERS.(6, 25-27) The HUNT study is based on a series of health surveys where the entire population of Nord-Trøndelag County, Norway, from 20 years of age has been invited to participate. The first survey was conducted in 1984-1986 (HUNT 1), the second survey in 1995-1997 (HUNT 2), and the third survey in 2006-2008 (HUNT 3). In all surveys a basic questionnaire was accompanying the invitation letter and the participants were asked to meet at screening stations for clinical and laboratory examinations. A short questionnaire (Mini-Q) was sent to non-participants after HUNT 3 in 2009 and those who responded to the Mini-Q were also included in our study. The questionnaires and examinations included a wide range of health related topics.(28)

Assessment of the outcome gastroesophageal reflux symptoms

In HUNT 2 and HUNT 3/Mini-Q, GERS status of the participants was defined based on the participants' response to the following question: 'To what degree have you had heartburn or acid regurgitation during the previous 12 months?' The question had three response alternatives: 'No complaints', Minor complaints', or 'Severe complaints'. Improvement in GERS status from severe GERS in HUNT 2 to no or minor GERS in HUNT 3/Mini-Q was defined as the study outcome, while severe GERS at both time points (stable GERS) were defined as reference. We have previously validated this GERS question and found that 25% to 31% of those reporting minor GERS and 95% to 98% of those reporting severe GERS had at least weekly complaints.(25) This suggests that the majority of those reporting severe GERS actually have GERD according to the Montreal definition and classification of GERD.(25, 26, 29)

Assessment of the exposure tobacco smoking

In HUNT 2, the participants were asked about their tobacco smoking status by answering yes or no to these questions: 'Have you ever smoked daily?', 'Do you smoke cigarettes daily?', 'Do you smoke cigars or cigarillos daily?', and 'Do you smoke pipe daily?' In HUNT 3/Mini-Q, the participants were asked: 'Do you smoke?' The response alternatives to this question were: 'No, I have never smoked', 'No, I have quit smoking', 'Yes, cigarettes occasionally (parties/vacation, not daily)', or 'Yes, cigarettes daily'. Those who quitted daily tobacco smoking or reduced daily smoking to only occasional smoking between HUNT 2 and HUNT 3/Mini-Q were defined as 'exposed' to tobacco smoking cessation, and those who were persistent daily tobacco smokers at both time points were regarded as 'unexposed' to such cessation.

Assessment of co-variables

Co-variables were selected based on their known association with GERS: sex, age, alcohol consumption, education, physical exercise, body mass index (BMI), and antireflux medication. Data on sex and age at participation were recorded at each survey. Average frequency of alcohol consumption and physical exercise was reported through questionnaires in HUNT 3/Mini-Q. Years of education were reported through questionnaires in HUNT 2. BMI was assessed by objectively measuring height and body weight under standardized conditions and by trained personnel at the screening stations in HUNT 2 and HUNT 3, while in Mini-Q height and weight were reported by the responders. BMI was calculated as body weight in kilograms divided by the square height in meters (kg/m^2). Antireflux medication included proton pump inhibitors (PPIs), histamine-2-reseptor antagonists (H2RAs), and antacids. In Norway, the prescription rules have until 2010 demanded a prescription from a physician to get PPIs or H2RAs, except small packages of low dose H2RAs which

have been available over the counter (OTC). In this study, information was gathered on the participants' use of prescribed antireflux medication through the Norwegian Prescription Database (NorPD). The NorPD was established in 2004, and all prescribed medications from all Norwegian pharmacies were by legislation reported to the NorPD. From the NorPD data, the average use of prescribed antireflux medication was estimated based on number of tablets prescribed during the HUNT 3 data collection period (2006-2008). In addition, the questionnaires in HUNT 3 included an assessment of OTC medication use against several complaints, including heartburn or acid regurgitation. The question was: 'How often have you used over the counter medication against the following complaints during the last month?' The participants responded with one of four alternatives to this question: 'Rare/never', '1-3 times/week', '4-6 times/week', or 'Daily'. Thus, the two data sources were complementary regarding the use of antireflux medication. There was no information on antireflux medication available during the HUNT 2 period.

Statistical analysis

Response rates were calculated from those eligible to participate at each survey, excluding those who were no longer residents in the county or had died. The association between tobacco smoking cessation (exposure) and GERS status (outcome) was assessed by multivariable logistic regression. Based on acknowledged criteria of a confounding factor, antireflux medication should not be included in the regression model, but instead be assessed as an effect modifier.(30) To account for the effect of antireflux medication on GERS, the analyses were stratified by the use of antireflux medication, no or less than weekly use and at least weekly use, and the results were reported for each stratum separately. Participants with missing information on antireflux medication were analyzed as using no or less than weekly antireflux medication, because in the NorPD data it was not possible to distinguish between those with truly missing data and those who did not receive a prescription. Secondary analyses were also stratified by BMI using the categories defined by the

World Health Organization (WHO): <18.5 units (underweight), 18.5-24.9 units (normal weight), 25.0-29.9 units (pre-obese), and ≥30.0 units (obese).(31) To account for other potential confounders in the association between tobacco smoking and GERS, a continuous variable for age and categorical variables for sex, alcohol consumption (<weekly or ≥weekly), education (≤12 years or >12 years), and physical exercise (<weekly or ≥weekly) were included in the regression model. The statistical analyses were performed using Stata/IC 12.1 by StataCorp LP.

Study approval

The study was approved by the Regional Committee for Medical and Health Research Ethics, Central-Norway (ID 4.2009.328).

RESULTS

Participants

We have previously published a complete flowchart of the participants.(26) In HUNT 2 and HUNT 3/Mini-Q, 58,869 individuals (64% response rate) and 44,997 individuals (49%) reported GERS status, respectively. Among these, the 29,610 individuals (61%) who reported GERS status at both time points were eligible. The average follow-up time was approximately 11 years. Among the 1553 participants with severe GERS (5%) in HUNT 2, the 486 (31%) who were daily tobacco smokers were included in the present study. Of these participants, 182 quitted smoking and 31 reduced to occasional smoking. In total, 213 (44%) were previous daily smokers while 251 (52%) were persistent daily smokers in HUNT 3/Mini-Q. In both these groups, about 60% were using antireflux medication at least weekly (Figure 1). The mean BMI was similar between the groups, but obesity was less common among the persistent daily smokers. Compared to the previous daily smokers, the persistent daily smokers were characterized by higher female representation, lower mean age, lower education, lower level of physical exercise, and lower alcohol consumption (Table 1).

Associations

Among the daily tobacco smokers with severe GERS in HUNT 2 using no or less than weekly antireflux medication, there was no statistically significant association between tobacco smoking cessation and GERS status (adjusted OR 0.95, 95% CI 0.39 to 2.30), compared with persistent daily smoking (Table 2). However, among the daily tobacco smokers with severe GERS in HUNT 2 using at least weekly antireflux medication, tobacco smoking cessation was associated with an improvement in GERS status from severe to no or minor complaints (adjusted OR 1.78, 95% CI 1.07 to 2.97), compared with persistent daily smoking (Table 2). Secondary, subgroup analyses found that the association only was present among individuals within the normal weight range (adjusted OR 5.67, 95% CI 1.36 to 23.64),

but not among overweight individuals (Table 3 and Figure 2). There was no association between tobacco smoking cessation and GERS status among individuals with minor GERS in HUNT 2 (data not shown).

DISCUSSION

This study found that tobacco smoking cessation was associated with an improvement in severe GERS among normal weight individuals using antireflux medication at least weekly. There was, however, no such pattern in individuals with minor GERS, overweight, or those using antireflux medication less than weekly.

Strengths of this study include the population-based design, reducing selection bias and increasing generalizability compared with clinic-based studies. Except for slightly lower average income and education and lack of a large city, the population of Nord-Trøndelag County is representative of the Norwegian population at large.(28, 32) In addition, the prospective design circumvents recall bias and the wide range of variables assessed, including antireflux medication, makes adjustments for relevant confounders possible. Limitations include the inherent arbitrary definition of GERD, reducing the accuracy of identifying individuals with true GERD, probably leading to some misclassification. Misclassification is also possible among the exposure and co-variables, as the variables were dichotomized. In addition, the associations found were only modest and residual confounding can never be totally excluded in observational research. Loss to follow-up may introduce selection and survival bias, but such potential biases are probably small as a previous publication has shown that there was virtually no difference in the distribution of the study variables between all the HUNT 2 participants (N=58,869) and the cohort who was followed up from HUNT 2 to HUNT 3 /Mini-Q (N=29,610).(27) Due to the observational design, causal relationships cannot be claimed. As there were low numbers of missing data among the participants (Table 1), complete case analyses were performed.

The three previous studies addressing smoking cessation and GERD found conflicting results. One study found no influence of 24 hours refrainment from smoking on 24-hour pH-measurements of the

distal esophagus in 10 smokers with GERS.(22) Another study found no immediate effect of smoking cessation on total esophageal acid exposure in 8 smoking men with moderate to severe endoscopic evidence of GERD. (23) The third study, however, found a reduced distal esophageal acid exposure in 14 smokers with reflux esophagitis who abstained from smoking for 48 hours.(24) Our study is the first epidemiological investigation testing whether tobacco smoking cessation improves GERS and the first study that evaluates such cessation in a long-term perspective.

The results of our study suggest that tobacco smoking cessation may improve severe GERS among normal weight individuals in the general population. As this is an observational study, a causal relationship cannot be claimed, and we do not know if smoking cessation occurred before improvement of GERS or the other way around. However, the results are consistent with the pathophysiology (10-14) and a randomized controlled trial of smoking cessation would be very hard and unethical to perform. The study only considered frequency of tobacco smoking, not dose or time since cessation. However, pathophysiological data suggests that the effect of tobacco smoking is very short lived, so dose and time since cessation should be of less importance. In addition, daily smoking is a common cut-off level in observational study, making comparisons with other studies easier. We found no association between tobacco smoking cessation and improvement in minor GERS. This probably reflects the heterogenetic nature of individuals reporting minor GERS, including individuals with functional syndromes. These syndromes have other pathophysiological mechanisms, at least partly not related to gastroesophageal reflux or tobacco smoking. Due to the low absolute number of individuals, we defined the 'exposure' in this study to be a combination of those quitting smoking and those only reducing daily smoking to occasional smoking. Even so, we found an association between the 'exposure', i.e. reduced tobacco smoking, and the outcome, i.e. improved GERS. This suggests that total smoking cessation would increase the chance of success even more than apparent from our study. The improvement in GERS was limited to persons of normal weight using at least

weekly antireflux medication. The lack of improvement in overweight individuals might be explained by the strong association between BMI and GERS, which might dominate compared to the effect of tobacco smoking on GERS in overweight individuals. Thus, the pathophysiology of GERS is probably driven by the weight in overweight and obese individuals and smoking has a minor role, but in individuals of normal weight smoking has a more important role in the pathophysiology. The lack of improvement among those using no or less than weekly antireflux medication, suggests that the individuals with severe GERS have an advanced stage of GERD, i.e. esophagitis or symptoms related to the presence of hiatal hernia, which does not resolve only with tobacco smoking cessation. However, weight loss and tobacco smoking cessation might reduce the need for antireflux medication over time. In addition, these lifestyle measures are also advisable due to the effects on general health. As tobacco smoking as well as GERS is associated with adenocarcinoma of the distal esophagus and gastric cardia, persons with GERS should be advised to refrain from smoking.(16-19) The population-based design, argues for generalizability to the general Norwegian population and other Western populations of mainly Caucasians.

In conclusion, while tobacco smoking cessation was not associated with any decrease in GERS among individuals with minor GERS, overweight, or those using antireflux medication less than weekly, an improvement in severe GERS was identified among normal weight individuals using regular antireflux medication. Tobacco smoking cessation might be beneficial in this latter group of patients suffering from gastroesophageal reflux.

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CONFLICT OF INTEREST/STUDY SUPPORT

GUARANTOR OF THE ARTICLE

EN-J accepts full responsibility for the conduct of the study and had access to the data and control of the decision to publish.

SPECIFIC AUTHOR CONTRIBUTIONS

EN-J has provided substantial contributions in planning and conducting the study, interpreting data, drafting the manuscript, and he has approved the final draft submitted. AL has provided substantial contributions in planning and conducting the study, interpreting data, drafting the manuscript, and she has approved the final draft submitted. JL has provided substantial contributions in planning and conducting the study, interpreting data, drafting the manuscript, and he has approved the final draft submitted. KH has provided substantial contributions in planning and conducting the study, collecting and interpreting data, drafting the manuscript, and he has approved the final draft submitted.

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POTENTIAL COMPETING INTERESTS

None

FIGURE LEGENDS

Figure 1 Flowchart of study participants

Figure 2 Odds ratio and 95% confidence interval (CI) of improvement in severe GERS by tobacco smoking cessation, comparing previous daily tobacco smokers with persistent daily tobacco smokers as reference. Restricted to those using *at least weekly* antireflux medication and stratified by body mass index (BMI). Model adjusted for sex, age, alcohol consumption, education, and physical exercise.

TABLES

Table 1 Characteristics of study participants

Tobacco smoking status	**Previous daily smokers** (n=213)		**Persistent daily smokers** (n=251)	
	No or < weekly	**≥ Weekly**	**No or < weekly**	**≥ Weekly**
Antireflux medication*	(n=86)	(n=127)	(n=99)	(n=152)
BMI†				
Mean (sd)	28.5 (4.7)	29.2 (4.5)	28.1 (5.0)	28.9 (5.1)
Median (range)	28.1 (18.7-47.2)	29.0 (19.0-44.1)	27.8 (18.9-49.3)	28.0 (15.2-47.5)
< 18.5, no. (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.3)
18.5-24.9, no. (%)	22 (25.6)	20 (15.7)	28 (28.3)	30 (19.7)
25.0-29.9, no. (%)	35 (40.7)	55 (43.3)	42 (42.4)	69 (45.4)
≥ 30.0, no. (%)	29 (33.7)	49 (38.6)	28 (28.3)	51 (33.6)
Missing, no. (%)	0 (0.0)	3 (2.4)	1 (1.0)	0 (0.0)
Sex, no. (%)				
Women	37 (43)	54 (43)	52 (53)	92 (61)

Age, years				
Mean (sd)	55.7 (11.7)	58.9 (9.9)	51.8 (10.3)	57.5 (10.3)
Median (range)	55.3 (32.8-84.9)	58.6 (34.3-84.7)	51.3 (34.1-84.4)	56.7 (31.9-87.8)
Alcohol consumption, no. (%)				
< Weekly	51 (59.3)	82 (64.6)	65 (65.7)	107 (70.4)
≥ Weekly	34 (39.5)	44 (34.6)	34 (34.3)	44 (28.9)
Missing	1 (1.2)	1 (0.8)	0 (0.0)	1 (0.7)
Education, no. (%)				
≤ 12 years	67 (77.9)	112 (88.2)	91 (91.9)	135 (88.8)
> 12 years	17 (19.8)	13 (10.2)	7 (7.1)	14 (9.2)
Missing	2 (2.3)	2 (1.6)	1 (1.0)	3 (2.0)
Physical exercise, no. (%)				
< Weekly	28 (32.6)	33 (26.0)	38 (38.4)	56 (36.8)
≥ Weekly	58 (67.4)	92 (72.4)	61 (61.6)	94 (61.8)
Missing	0 (0.0)	2 (1.6)	0 (0.0)	2 (1.3)

* Antireflux medication: proton pump inhibitors, histamine-2-receptor antagonists, and antacids

Participants with no information on antireflux medication were included in never or < weekly category

† BMI: body mass index (kg/m2)

Table 2 Odds ratio (OR) with 95% confidence interval (CI) of improvement in severe GERS by tobacco smoking cessation, stratified by use of antireflux medication*

	Unadjusted			Adjusted for sex and age			Fully adjusted†		
Antireflux medication‡	**No.**	**OR**	**95% CI**	**No.**	**OR**	**95% CI**	**No.**	**OR**	**95% CI**
No or < weekly	185	1.12	0.48 - 2.62	185	1.06	0.45 - 2.52	181	0.95	0.39 - 2.30
≥ Weekly	279	1.44	0.90 - 2.32	279	1.62	0.99 - 2.65	268	1.78	1.07 - 2.97

* From severe heartburn or acid regurgitation (GERS) in HUNT 2, to no or minor GERS in HUNT 3/Mini-Q

Comparing previous daily smokers with persistent daily smokers as reference

† Adjusted for sex, age, body mass index, alcohol consumption, years of education, and physical exercise

‡ Antireflux medication: proton pump inhibitors, histamine-2-receptor antagonists, and antacids

Table 3 Odds ratio (OR) with 95% confidence interval (CI) of improvement in severe GERS by tobacco smoking cessation, stratified by use of antireflux medication and body mass index (BMI)*

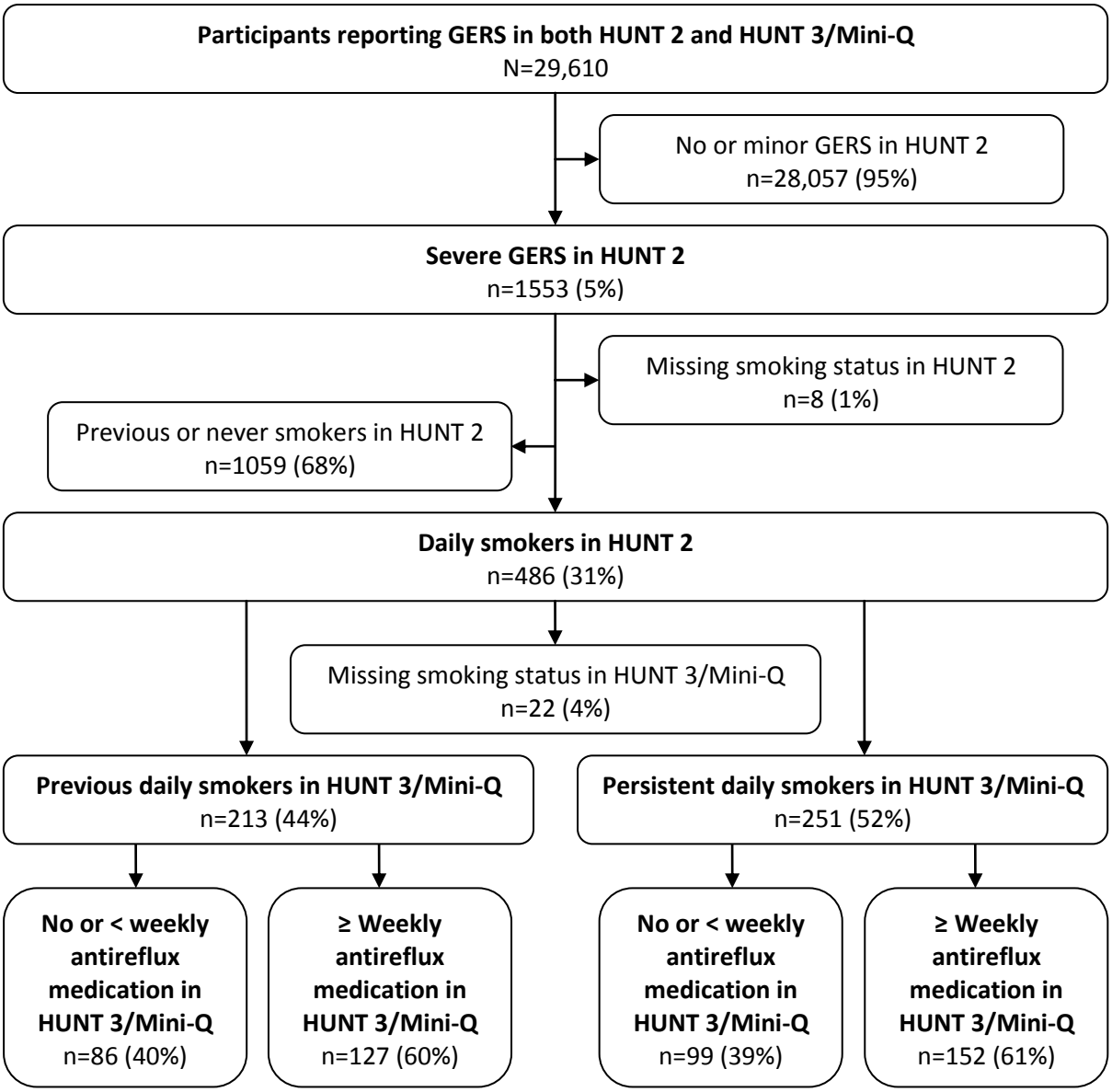
		Unadjusted			Adjusted for sex and age			Fully adjusted†		
Antireflux medication‡	**BMI**	**No.**	**OR**	**95% CI**	**No.**	**OR**	**95% CI**	**No.**	**OR**	**95% CI**
No or < weekly	**All**	185	1.12	0.48 - 2.62	185	1.06	0.45 - 2.52	181	0.95	0.39 - 2.30
	18.5-24.9	50	1.06	0.21 - 5.30	50	0.89	0.17 - 4.65	49	0.80	0.13 - 5.08
	25.0-29.9	77	1.29	0.33 - 5.00	77	1.32	0.33 - 5.27	63	1.13	0.27 - 4.75
	≥ 30.0	57	1.04	0.23 - 4.64	57	0.74	0.14 - 3.89	57	0.90	0.16 - 5.17
≥ Weekly	**All**	279	1.44	0.90 - 2.32	279	1.62	0.99 - 2.65	268	1.78	1.07 - 2.97
	18.5-24.9	50	3.92	1.13 - 13.60	50	4.70	1.22 - 18.18	49	5.67	1.36 - 23.64
	25.0-29.9	124	1.25	0.62 - 2.56	124	1.20	0.57 - 2.53	121	1.24	0.57 - 2.71
	≥ 30.0	100	1.01	0.46 - 2.22	100	1.28	0.55 - 2.99	93	1.29	0.53 - 3.17

* From severe heartburn or acid regurgitation (GERS) in HUNT 2, to no or minor GERS in HUNT 3/Mini-Q

Comparing previous daily smokers with persistent daily smokers as reference

† Adjusted for sex, age, alcohol consumption, years of education, and physical exercise

‡ Antireflux medication: proton pump inhibitors, histamine-2-receptor antagonists, and antacids


Participants reporting GERS in both HUNT 2 and HUNT 3/Mini-Q
N=29,610
No or minor GERS in HUNT 2
n=28,057 (95%)
Severe GERS in HUNT 2
n=1553 (5%)
Missing smoking status in HUNT 2
n=8 (1%)
Previous or never smokers in HUNT 2
n=1059 (68%)
Daily smokers in HUNT 2
n=486 (31%)
Missing smoking status in HUNT 3/Mini-Q
n=22 (4%)
Previous daily smokers in HUNT 3/Mini-Q
n=213 (44%)
Persistent daily smokers in HUNT 3/Mini-Q
n=251 (52%)
No or < weekly antireflux medication in HUNT 3/Mini-Q
n=86 (40%)
≥ Weekly antireflux medication in HUNT 3/Mini-Q
n=127 (60%)
No or < weekly antireflux medication in HUNT 3/Mini-Q
n=99 (39%)
≥ Weekly antireflux medication in HUNT 3/Mini-Q
n=152 (61%)

All
18.5-24.9
25.0-29.9
≥ 30.0
BMI (kg/m^2)
0.1
0.5
1
5.0
10
30
Odds ratio (95% CI)